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EXAMINER	
MAYER, SUZANNE MARIE	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 05/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,428	VLODAVSKY ET AL.	
	Examiner	Art Unit	
	Suzanne M. Mayer, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *38-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-0-0.

DETAILED ACTION

Claim Status

1. Claims 38-49 are pending. Claims 1-37 have been cancelled by Applicant.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on March 5, 2005 has been considered by the examiner. See attached and signed PTO-1449.

Specification

3. The disclosure is objected to because of the following informalities: on p. 37, paragraphs [000158-000159] it is stated that Major Basic Protein (MBP) is purified according to Slifmen et al. 1986. However, the Examiner notes that Slifmen et al. **did not** purify MBP, rather Slifmen et al. purified Eosinophil-Derived Neuroxtoxin (EDN) and Eosinophil Cationic Protein (ECP).

Appropriate correction is required.

Withdrawl of Rejections/Objections

4. All 35 U.S.C. §112 2nd paragraph rejections are withdrawn.

5. 35 U.S.C. §112 1st paragraph – Enablement; the first two enablement rejections are withdrawn. (Sections 7 and 8 of the previous Office action).

6. 35 U.S.C. §112 1st paragraph – Written Description; the first written description rejection is withdrawn (Section 10 of the previous Office action).

7. 35 U.S.C. §102(b); the claims rejection over Futura et al. is withdrawn (Section 14 of the previous Office action).

Maintained Rejections

8. The rejections that follow reflect the new claims and claim numbers. Previously presented but now cancelled Claims 1-13 are commensurate in scope with new claims 38-41; Previously presented but now cancelled Claims 16-19 are commensurate in scope with new claims 42-45; Previously presented but now cancelled Claims 30-33 and 35-37 is commensurate in scope with new claims 46-48; Previously presented but now cancelled Claims 14-15 are commensurate in scope with new claim 49

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

10. Claims 42-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of treating a subject by inhibiting heparanase glycosidase activity by administering an effective amount of any one of eosinophil secondary granules protein, which includes major basic protein (MBP). It is well documented and known in the art that eosinophils are cytotoxic. For example, Furuta et al. describe eosinophils as such: "Eosinophils normally reside in tissues with mucosal surfaces such as the gastrointestinal tract. A variety of inflammatory and allergic diseases, including inflammatory bowel disease (IBD), parasitic infections, eosinophilic gastroenteritis, asthma, atopic dermatitis, and allergic rhinitis are associated with increases in the number of eosinophils within affected tissues". Thus how the administration of cytotoxic proteins to a subject and which will not elicit an inflammatory immune system response while still functioning to inhibit heparanase glycosidase activity is unclear because the concentration necessary for inhibition of a heparanase glycosidase activity may exceed the lowest levels of detection in the subject.

The factors to be considered in determining whether undue experimentation is required are summarized above in paragraph 8. The quantity of testing in order to determine if administration of a pharmaceutical composition that comprises, for example MBP, and whether or not the concentration that is administered to a subject not only inhibits heparanase activity but also elicits an adverse and negative immune response in the patient is considerable because the use of this protein for this heparanase effect has never been considered in the prior art. The only examples in the prior art are drawn

to methods of inhibiting eosinophils and the immune response that they cause, and not to administering them to a subject. The specification does not even address this issue what so ever so there is zero guidance in how a skilled artisan should have to deal with such a situation. The only working example present is drawn to administration of MBP in a mice, but again it is not addressed what the appropriate protocol might be to avoid an adverse immune response. Further, it seems that no testing was done on this matter in the mice which were administered MBP. The nature of the invention is such that it may put subjects at risk for adverse immune responses which may be lethal to some. The relative skill of those in the art is exceedingly high and the predictability of whether the administration of the composition will adversely affect the subjects due to an inflammatory immune response is huge.

When the factors are considered in their entirety, the Wands analysis dictates a finding of undue experimentation and thus, the claim is not enabled.

Written Description

11. Claims 3, 5-28, and 35-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to the inhibition of heparanase glycosidase activity *in vivo* and *in vitro*.

Examples of *in vitro* inhibition of heparanase is given in Figure 5, and the effective concentrations also stated for MBP, EPO, EDN and ECP. However, no examples for poly-L-arginine, the effective of amount used for eosinophil lysates in Figure 5, or any combinations of MBP, EPO, ECP, and EDN, a fusion protein, a nucleic acid construct encoding the protein, a host cell expressing said construct, a cell, a cell line and/or tissue endogenously expressing the protein(s). Thus it is unclear how applicant was in possession of the invention as claimed when the working examples are limited to MBP, EPO, and ECP, separately and not in combination with one another.

Vas-Cath Inc. V. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed."* The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." As discussed above, the skilled artisan cannot envision the amount sufficient to inhibit heparanase glycosidase activity when using MBP, ECP or EPO, a fusion protein, a nucleic acid construct encoding the protein, a host cell expressing said construct, a cell, a cell line and tissue endogenously expressing the protein(s) and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the methods of making the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating or making it. The compound

itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Claim Rejections - 35 USC § 102

12. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

13. Claims 38-41 are rejected under 35 U.S.C. 102(a) as being anticipated by Davis et al. Davis et al. disclose a pharmaceutical composition containing EDN, ECP, MBP and EPO which is used to test the lower limits of detection on the skin for a subjects inflammatory immune response reaction. Thus the limitations of the claims have been met.

New Rejections

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting heparanase glycosidase catalytic activity in a subject in need thereof, does not reasonably provide enablement for inhibiting heparanase glycosidase catalytic activity to any or all subjects. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Amending the claim to recite 'a subject in need thereof' would overcome this rejection.

16. Claims 42-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of inhibiting heparanase glycosidase activity in a subject or *in vitro* by administering 1-180 μg/ml would require undue experimentation to see if it even works. It is well known in the medical community and to those skilled within the art that administration to a subject is nearly always dependent upon the weight of a subject. Thus, while the administration of 180 μg/ml to a 2 kg mouse, it is not going to be effective whatsoever in inhibiting heparanase glycosidase activity in for instance a 500 kg cow. Thus one of ordinary skill in the art would be required to experiment with effective concentrations for each and every different type of subject to which administration of eosinophil cell lysate or eosinophil secondary granular basic protein was given. Furthermore, the prior art is silent on this aspect as these types of proteins are not known to be heparanase glycosidase inhibitors and the amount of guidance in the specification is silent with appropriate dosage amounts. When all the factors are considered together, there is the finding of an undue burden and invitation to the skilled artisan to have to performs undue experiments in order to reduce Applicants claimed invention to practice.

Response to Arguments

17. The Examiner acknowledges and appreciates the amendment to the claims that more distinctly define the invention. Specifically, the recitation of which MBP that it intended for use in the claimed invention. Also the removal the objectional language involving fragments is also appreciated.

However, the rest of Applicant's arguments filed March 3, 2005 have been fully considered but they are not persuasive.

35 U.S.C. § 112

18. Applicant suggests that the new claims have been rewritten to comport more with the specification and as such shows that applicant had possession of the invention as claimed for claims 38-49. The examiner does concede that Applicant indeed does have in their possess and do show working examples of MBP and ECM. However, as this is such a novel and different method and use of the MCP, ECM, EDN and EPO (eosinophil peroxidase) proteins, what Applicant fails to show that they do have in their possession is proteins in mixtures with one another. Since this is such a divergent and novel use of these proteins it is not even known if these proteins can work in concert with one another, and if so, what are the effective concentrations per protein (and per kg weight of the subject) if for example, all four were used in a single composition, which is a limitation stated in the claims. Since there is no guidance or even suggestion in the specification other that it is a preferred embodiment, the Examiner can only assume that Applicant does not have this in their possession and the Examiner will continue to do so until evidence if otherwise introduced.

The Examiner further wishes to point out that in all of the Examples which utilize MBP and else where in the specification, that a generalized statement is used that MBP is formulated in a pharmaceutically acceptable carrier. However, since it is well known in the art that MBP in not very soluble at neutral pH's, exactly which pharmaceutical formulations (e.g. liposome's) constitute and make MBP usable at neutral pH's. The specification is likewise silent on this aspect.

19. Applicants contend that by Example 3 in the specification, which describes how MBP was able to inhibit a number of metastatic colonies in the lungs of mice injected with B16 melanoma cells. And also that "the specification gives ranges that are sufficient to inhibit heparanase activity..... and that furthermore, that the mice treated with MBP were viable, and most importantly showed no adverse or negative immune response (unpublished Inventor's data)." However, the Examiner and the rest of the public have no way of knowing this, because as Applicant has pointed out, it is no where to be found in the specification or else where. Once it is made of record, the matter will be readdressed.

35 U.S.C. § 102

20. The rejection under 102(b) has been withdrawn, however, the rejection under 102(a) remains. Applicants argue that the Davis et al. reference is not concerned with the problem concerning the present invention and that whatever compositions may be disclosed that they do not meet the limitations of the present invention and also that the reference does not suggest the composition claimed or the use to which it is put for advantage.

The Examiner respectfully disagrees with these assertions. Davis et al. do teach MBP, ECM, ECP and EPO in the concentration range of 0.001 – 50.0 μmol/L (see p. 989, 2nd column 1st paragraph) and in a diluent, namely PBS (a known neutral buffer).

Furthermore, the examiner does not find Applicants arguments persuasive regarding that the composition of Davis et al. do not suggest that the composition is not taught for the use for which it is to be put for advantage in the present invention. This is unpersuasive because the mere introduction of the intended use language recited in the pre-amble does not hold any definitive patentable weight as the preamble in the instant case does not breathe life and meaning into the claims. See for example, *Corning Glass Works,* 868 F.2d at 1257, 9 USPQ2d at 1966. If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). See also *Rowe v. Dror*, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997) ("where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation").

Conclusion

21. No claim is allowed.

22. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Mayer, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 8.30am to 5.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SMM
20 May 2005

ROBERT A. WAX
PRIMARY EXAMINER
Art Unit